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Two Sibs With Anophthalmia and Pulmonary Hypoplasia (the Matthew-Wood Syndrome)

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We describe two sibs with pulmonary hypoplasia and anophthalmia; one also had a number of other malformations. Only one other broadly similar case could be found in the literature, and it was an isolated occurrence. The condition is named the Matthew-Wood syndrome. © 1996 Wiley-Liss, Inc.

KEY WORDS: lung, eye, anophthalmia, malformations

INTRODUCTION

An/microphthalmia is well recognized as a heterogeneous malformation. Primary pulmonary agenesis/hypoplasia is also known, although rare, and three sibships are recorded [Boylen et al., 1977; Toriello et al., 1985; Fraser, 1994], but most of the cases appear sporadically. There are three instances of anophthalmia and pulmonary hypoplasia occurring together in the same individual [Östör et al., 1978; Toriello and Bauserman, 1985; Spear et al., 1987], and all were isolated cases, and there was a variety of other defects. We report on two sibs with anophthalmia and primary pulmonary hypoplasia; the first had no other abnormality, but the second had several other defects.

CLINICAL REPORT

The first child of a healthy non-consanguineous Caucasian couple ages 35 and 36 years died 1 hour after birth. Fetal chromosome studies had been undertaken during the pregnancy, and a normal male karyotype found. The delivery was induced at 38 weeks of gestation for pre-eclampsia. The male infant (Fig. 1) weighed 2,860 g and he had recessed orbits and barely opened palpebral fissures, but was otherwise outwardly normal; however, he survived for only 1 hour. Autopsy showed bilateral anophthalmia, the orbits contained principally fat tissue, and, posteriorly, the termination of their optic nerves. The brain and optic nerves were developmentally normal but there were generalized subarachnoid and interventricular hemorrhages. The upper respiratory tract, trachea and main bronchi were normal, but the lungs were unilobar and the morphology indicated that only the lower lobes of each were present and the upper lobes were absent. The liver was normal except for a sharp demarcation into three lobes on the upper surface, but this division did not extend deeply into the substance of the liver. There were no other abnormalities.

The findings did not fit any recognized syndrome. There was nothing remarkable in the family history, so in view of the heterogeneity of anophthalmia and uncertainty about the significance of the associated pulmonary hypoplasia the parents were given a recurrence risk of around 1 in 10 to 1 in 15, and offered detailed ultrasound scanning in subsequent pregnancies.

Chorionic villus sampling in the second pregnancy showed a 46,XY karyotype. Scanning suggested no abnormalities, and a normal boy was delivered who is alive and well. In the third pregnancy, a normal female chromosome complement was found following amniocentesis, but the scan showed bilateral anophthalmia and hypoplastic lungs. The parents requested termination of pregnancy.

The female fetus, foot length 25 mm, equivalent to 18 weeks of gestation, had a slender, rather emaciated appearance and weighed 109 g (expected weight for 18 weeks around 130 g). The orbits were recessed (Fig. 2) and there was bilateral anophthalmia. The palpebral fissures could not be opened and they were relatively close together in the midline. The nose was narrow but made prominent by a pointed upturned tip, and the alae nasi were hypoplastic. The upper lip was short; the maxilla was prominent (Fig. 3) and overhung the mouth. There was micrognathia and a midline cleft of the posterior part of the secondary palate. The ears were apparently low-set and flat and there was brachycephaly. The thumbs had bulbous tips, but there were no other external abnormalities.

Internally, there was bilateral, but asymmetric, hypoplasia of the lungs: moderate hypoplasia on the left,

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Fig. 1. Frontal view of face of first child showing recessed orbits and barely-opened palpebral fissures.

more severe on the right, and there was no obvious lobulation. The heart had a single ventricle, a markedly hypoplastic left atrium, and an enlarged pulmonary trunk. The spleen was markedly hypoplastic and the uterus was bicornuate and hypoplastic. All other internal organs appeared grossly normal. The brain was severely autolysed, but was apparently normal; and the olfactory bulbs and optic nerves were present.

Lymphocyte karyotypes of both parents were normal.

DISCUSSION

The findings in these two sibs are consistent with a genetic condition inherited in an autosomal recessive manner, which has variable expressivity, with the main anom

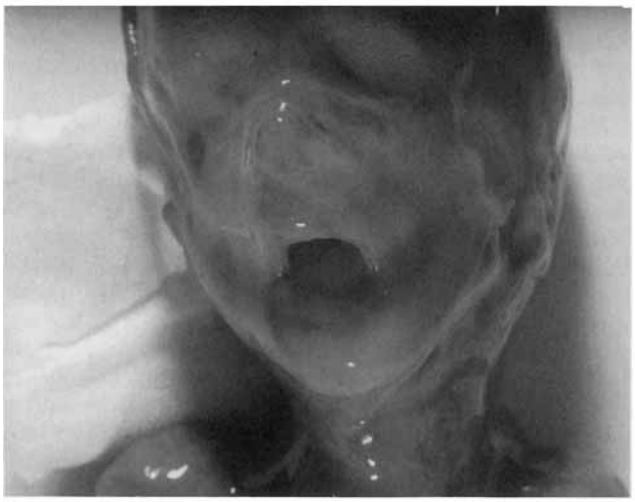

Fig. 2. Frontal view of face of 18 week fetus showing recessed orbits, closed palpebral fissures relatively close together, prominent nose with upturned tip and hypoplastic alae nasi, and short upper lip.

anophthalmia. It appears similar to the case of Spear et al. [1987] with pulmonary agenesis, microphthalmia, ventricular septal defect, and eventration of the left diaphragm, but different from that of Toriello and Bauserman [1985], where many stigmata of the hydrolethalus syndrome including marked hydrocephalus and micrognathia were also present. It is also probably not the same as the patient described by Östör et al. [1978], who had in addition frontal encephalocele, duodenal atresia, renal dysplasia, an accessory spleen, and four normal sibs.

It seems generally accepted that pulmonary agenesis and primary pulmonary hypoplasia and abnormal lung lobulation are part of the same spectrum of developmental defects, as are microphthalmia and anophthalmia. Isolated microphthalmia is often inherited in an autosomal recessive manner, but dominant forms are known. Microphthalmia and pulmonary agenesis can each be found in conjunction with other abnormalities, the former as part of Fraser syndrome, Goldenhar syndrome and anophthalmia-type Waardenberg, but these syndromes do not resemble our cases. Some of the defects recorded as associated with cases of pulmonary agenesis are consistent with those found in the second child: congenital heart defects, uterine anomalies, and either absent or an accessory spleen, although a variety of other defects is found [Toriello et al., 1985]. The combination of an/microphthalmia and lung hypoplasia may occur as part of a number of syndromes (Table I) but clearly these were readily excluded.

In developmental terms it is difficult to explain the concurrence of these two major defects arising from the mutation of a single gene. It is easier to think in terms of a contiguous gene syndrome. Both major defects individually can be found associated with particular chromosome abnormalities. Lurie et al. [1995] reviewed 50 cases of partial trisomy 2p and found certain common

Fig. 3. Lateral view of same fetus showing prominent maxilla, micrognathia and flat, low-set ears.

TABLE I. Syndromes Which Include a Combination of An/Microphthalmia and Pulmonary Hypoplasia*

Carpenter-Hunter: micromelia, polysyndactyly, encephalocele, fragile bones
Encephalocele-radial, cardiac, gastrointestinal, anal and renal anomalies
Fryns: acral defects, cloudy corneae, diaphragmatic defects
Hanson: colobomas, unilobar lungs, atrioventricular septal defect
Hydrocephaly with features of VATER
Hydrolethalus
Meckel-Gruber
Renal-hepatic-pancreatic dysplasia with Dandy-Walker cyst
Van Allen-Myhre: ectopia cordis, split-hand/foot, skin defects
Zimmer: tetra-amelia with multiple malformations

* Source: London Dysmorphology Database: Oxford University Press, 1993.

manifestations although a variable phenotype, with some additional major malformations not usually observed in chromosomal syndromes. These included four instances of malformed lungs: two cases of unilateral pulmonary agenesis [Say et al., 1980; Schober et al., 1983] and two of primary lung hypoplasia with abnormal lobulation [Monteleone et al., 1981; Fryns et al., 1986]. Another partial trisomy 2p case had eye defects (anterior segment mesenchymal dysgenesis) [Heathcote et al., 1991] and a non-karyotyped sib of a trisomy 2p patient had anophthalmia [Carrière, 1975]. Weaver et al. [1991] reported a patient with a de novo pericentric inversion of chromosome 2 and bilateral microphthalmia and cataracts, and in reviewing the literature they found that seven of eight patients with deletions on 2p had eye defects, although none involved microphthalmia. Yokoyama et al. [1992] reported on a family with a 2:16 translocation with one of the breakpoints at 2p21 associated with microphthalmia and cataracts. No chromosome abnormalities were noted in our cases, or in the parents, despite a careful search, but this does not exclude the possibility of a tiny rearrangement, or microdeletion which could be present in both children as a result of parental gonadal mosaicism.

However, overall we think it most likely that this is the same condition as reported by Spear et al. [1987] but the presence of two affected sibs indicates that it is an autosomal recessive syndrome. The parents have requested that this be referred to as the Matthew-Wood syndrome.

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